REMARKS

The claimed methods (unlike the cited art) feature the direct coupling and integration of design and modeling software to the output from a high through-put (or parallel) instrument. The modeling methods in the art relied on by the Examiner fail to allow building a design model [QSAR] as an explicit function of multiple conformations, pharmacophore types and pharmacophore group locations within in molecule, as is accomplished by methods of the claims. In addition, none of the references relied on by the Examiner teach building a toxicity model as an explicit function of interacting the molecules with a model biological cellular membrane, as do claimed methods.

Claim Objections

The objection to claims 11 and 17 have been met by amending claims 11 and 17 as suggested by the Examiner.

35 USC § 112, first paragraph

Claims 1, 16 and 17 have been rejected as not enabled, see the paragraph bridging pages 4 and 5. The rejection is respectfully traversed.

The Examiner is concerned that the term "describing the interaction" would read on matters outside empirical determination, e.g., cost, availability, or esthetic matters, e.g., smell. A review of the entire claim shows that this is not the case. First the model requires "predicting one or more therapeutic properties" (see, e.g., the last line of claim 1). Second, the data describing the interaction must describe the interaction between two structures, a training compound and an interaction partner (see, e.g., the third and fourth lines of claim 1). Either of these limitations would exclude the sorts of parameters the Examiner has objected to. E.g., cost, availability or odor would not relate to an interaction between two structures.

35 USC § 112, second paragraph

Claims 8, 11-15 and 17 have been rejected as indefinite. The rejection of claims 11, 12, 13, 15 and 17 has been met by amending claims 8, 11 and 12. The rejection of claim 14 is

respectfully traversed. Caco-2 is not an abbreviation but the name of a type of cultured cells.

See page 45 of the specification, which provides:

> Caco-2 cells, a well-differentiated intestinal cell line derived from human colorectal carcinoma, display many of the morphological and functional properties of the *in vivo* intestinal epithelial cell barrier. Caco-2 cell models are used with regularity for determination of cellular transport properties, in both industry and academia, as a surrogate marker for *in vivo* intestinal permeability in humans.

35 USC § 102

Claims 1, 2, 6 and 16 are rejected as anticipated by Agrafiotis t al.

The rejection is met by amending claim 1. Agrafiotis et al. do not include the direct coupling of a high throughput property measuring instrument to a computational software package which transforms the collected data from the instrument into a model relating the measured properties to molecular features for designing new molecules.

35 USC § 103

Claims 1-6 and 16 are rejected as obvious over Agrafiotis et al. taken in view of Harrous et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed.

Agrafiotis et al do. not include the direct coupling of a high throughput property measuring instrument to a computational software package which transforms the collected data from the instrument into a model relating the measured properties to molecular features for designing new molecules.

Agrafiotis et al. merely deal with collecting property data from different sources and placing this data in a database that can be used at a later time as part of a larger software system. No direct coupling to a high throughput [parallel] system is stated or implied. The Agrafiotis et al. patent teaches at best) database management and use, not interfacing software to instruments.

The claimed method of transforming instrument data into a design model is unobvious, in part, because it explicitly considers the family of conformations, pharmacophore types and pharmacophore groups composing a molecule in the building and implementation of a design

model. Agrafiotis et al. present methods that, at best, sort through possible conformations of a molecule and selects only one for model building which is simplified representation of reality. Pharmacophore types and locations in a molecule are not explicitly considered in their model building schemes.

The Harrous et al. reference deals with computational work to evaluate the quality of data from a calorimeter, not to build design models. It does not suggest modification of Agrafiotis et al. to give the claimed invention. Agrafiotis et al. and Harrous et al do not teach the possibility, of explicitly considering multiple conformations, pharmacophore types and pharmacophore locations in a molecule in constructing a design model. Agrafiotis et al. do not separate biological properties into any types of classes and, thereby, do not recognize the unique difference between toxicity and therapeutic activity.

Claims 1, 2, 6, 7, 11 and 15-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al.

Claims 1, 2, 6, 7, 11 and 15-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al.

Claims 1, 2, 6, 7, 8, 9, 11 and 15-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al and Ekins et al.. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al. Ekins et al. is simply an application of 4D-QSAR and does not provide what the other references lack.

Claims 1, 2, 6, 7, 11 and 15-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al. and Khiat et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al. Khiat et al. is simply an application of NMR in SAR and does not provide what the other references lack

Claims 1, 2, 6, 7, 11-13 and 15-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al. and Klein et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al. Klein et al. does not add what these references lack. It is important to note that Klein et al. does not address the direct interfacing of design model software to the instrument. Rather, it deals only with collecting instrument property data, forming a database and subsequently analyzing it. The approach in Klein et al is largely similar to that in Agrafiotis et al.

Claims 1, 2, 6, 7, 11 and 13-17 are rejected as obvious over Agrafiotis et al. taken in view of Korzekwa et al. and Oprea et al. The rejection is met in part by amending claim 1 and is in part respectfully traversed. Agrafiotis et al. is discussed in detail above. Korzekwa et al. discusses ADMET but does not address the inadequacy of Agrifiotis et al. Oprea et al. merely discusses Caco-2 cells and does not add what the other references lack.

Applicant requests withdrawal of the rejections and allowance of the claims.

Enclosed is a check in the amount of $510.00 for the Petition for Extension of Time fee.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 27 May 05

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